



The
Patent
Office

PCT/US 98/14796

REC'D 13 AUG 1998

The Patent Office PCT
Concept House
Cardiff Road
Newport
South Wales
NP9 1RH

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT

Signed

Andrew Gersey

Dated

11 May 1998

BEST AVAILABLE COPY

The
Patent
Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You
an explanatory leaflet from the Patent Office
you fill in this form)

22 AUG 1997

The Patent Office

9717850.3

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

20002PV2

2. Patent application number

(The Patent Office will fill in this part)

3. Full name, address and postcode of the or of
each applicant (underline all surnames)

Merck & Co., Inc.
P. O. Box 2000
Rahway, New Jersey 07065-0900
U.S.A.

Patents ADP number (if you know it)

If the applicant is a corporate body, give the
country/state of its incorporation

New Jersey, USA

4. Title of the invention

Oral method for treating or preventing abnormal bone resorption

5. Name of your agent (if you have one)

Mr. I. J. Hiscock

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow
Essex CM20 2QR

Patents ADP number (if you know it)

06546683001

6. If you are declaring priority from one or more
earlier patent applications, give the country
and the date of filing of the or of each of these
earlier applications and (if you know it) the or
each application number

Country

Priority Application number
(if you know it)

Date of filing
(day/month/year)

7. If this application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing
(day/month/year)

8. Is a statement of inventorship and of right
to grant of a patent required in support of
this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an
applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

TITLE OF THE INVENTION

ORAL METHOD FOR TREATING OR PREVENTING ABNORMAL BONE RESORPTION

5 FIELD OF THE INVENTION

The present invention relates to oral methods for treating or preventing abnormal bone resorption in a mammal while minimizing the occurrence of adverse gastrointestinal effects. These methods comprise orally administering a pharmaceutically effective amount of a
10 bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. The method is continued until the desired therapeutic effect is achieved. The present invention also relates to pharmaceutical
15 compositions and kits useful in these methods.

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include,
20 but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and
25 microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

30 Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone

especially those relating to the esophagus. *See* Fleisch, Id. These effects appear to be related to the irritant potential of the bisphosphonate in the esophagus, a problem which is exacerbated by the presence of refluxed gastric acid. For example, the bisphosphonate, pamidronate
5 has been associated with esophageal ulcers. *See* E.G. Lufkin et al., *Pamidronate: An Unrecognized Problem in Gastrointestinal Tolerability, Osteoporosis International*, 4: 320-322 (1994). Although not as common, the use of alendronate has been associated with esophagitis and/or esophageal ulcers. *See* P.C. De Groen, et al.,
10 *Esophagitis Associated With The Use Of Alendronate, New England Journal of Medicine*, vol. 335, no. 124, pp. 1016-1021, 1058-1059, and 1069-1070 (October 3, 1996). The degree of adverse gastrointestinal effects of bisphosphonates has been shown to increase with increasing dose. *See* C.H. Chestnut et al., *Alendronate Treatment of the*
15 *Postmenopausal Osteoporotic Woman: Effect of Multiple Dosages on Bone Mass and Bone Remodeling, The American Journal of Medicine*, vol. 99, pp. 144-152, (August 1995). Also, these adverse esophageal effects appear to be more prevalent in patients who do not take the bisphosphonate with an adequate amount of liquid or who lie down
20 shortly after dosing, thereby increasing the chance for esophageal reflux.

Current oral bisphosphonate therapies generally fall into two categories: (1) those therapies utilizing continuous daily treatment, and
25 (2) those therapies utilizing a cyclic regimen of treatment and rest periods.

The daily treatment regimens normally involve the chronic administration of relatively low doses of the bisphosphonate compound, with the objective of delivering the desired cumulative therapeutic dose over the course of the treatment period. However, continuous daily
30 dosing has the disadvantage of causing adverse gastrointestinal effects due to the repetitive, continuous, and additive irritation to the gastrointestinal tract. Also, because bisphosphonates should be taken on an empty stomach followed by fasting and maintenance of an upright posture for at least 30 minutes, many patients find daily dosing to be

bisphosphonate compounds. Administration of a once weekly partial dose of the bisphosphonate is disclosed. However, the reference specifically fails to address the issue of adverse gastrointestinal effects or to disclose administration of larger or multiple dosages. It is seen
5 from current teachings that both daily and cyclic treatment regimens have shortcomings, and that there is a need for development of a dosing regimen to overcome these shortcomings.

In the present invention, it is found that the adverse gastrointestinal effects often associated with daily or cyclic dosing
10 regimens can be minimized by administering the bisphosphonate at a relatively high unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In other words, it is found that the administration of a
15 bisphosphonate at a high relative dosage at a low relative dosing frequency causes less adverse gastrointestinal effects, particularly esophageal effects, compared to the administration of a low relative dosage at a high relative dosing frequency. This result is surprising in view of the teachings suggesting that adverse gastrointestinal effects
20 would be expected to increase as a function of increasing bisphosphonate dosage.

From a patient lifestyle standpoint, the methods of the present invention would also be more convenient than daily or cyclic dosing regimens. Patients would be subjected less frequently to the
25 inconvenience of having to take the drug on an empty stomach and having to fast for at least 30 minutes after dosing. Also, patients would not need to keep track of a complex dosing regimen. The methods of the present invention are likely to have the advantage of promoting better patient compliance, which in turn can translate into better
30 therapeutic efficacy.

It is an object of the present invention to provide oral methods for treating abnormal bone resorption and the conditions associated therewith.

In other embodiments, the present invention relates to an oral method for treating or preventing osteoporosis in a mammal.

In other embodiments, the present invention relates to an oral method for treating or preventing abnormal bone resorption in a human
5 in need of such treatment comprising administering to said human from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

In other embodiments the present invention relates to a
10 pharmaceutical composition comprising from about 8.75 mg to about 140 mg, on an alendronic acid active basis, of a bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

All percentages and ratios used herein, unless otherwise indicated,
15 are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

BRIEF DESCRIPTION OF THE FIGURES

20 FIG. 1 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with five separate dosages of 50 mL of simulated gastric juice on five consecutive days.

25 FIG. 2 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with five separate dosages of 50 mL of 0.20 mg/mL alendronate in simulated gastric juice on five consecutive days.

30 FIG. 3 is a photomicrograph (total magnification 270X) of canine esophagus tissue (paraffin embedded and stained with hematoxylin and eosin) from an animal sacrificed 24 hours after infusion with a single dosage of 50 mL of 0.80 mg/mL alendronate in simulated gastric juice.

to esophagitis, esophageal ulcers, esophageal irritation, esophageal perforation, abdominal pain, gastric duodenal ulcers, and constipation.

5 The term "abnormal bone resorption", as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. Alternatively, "abnormal bone resorption" can be associated with the formation of bone having an abnormal structure.

10 The term "bone resorption inhibiting", as used herein, means preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

15 The terms "continuous schedule" or "continuous dosing schedule", as used herein, mean that the once-weekly, twice-weekly, biweekly, or twice-monthly dosing interval is repeated until the desired therapeutic effect is achieved. The continuous schedule or continuous dosing schedule is distinguished from cyclical or intermittent administration.

20 The term "until the desired therapeutic effect is achieved", as used herein, means that the bisphosphonate compound is continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition being treated is observed by the clinician or researcher. For methods of treatment of the present invention, the bisphosphonate compound is
25 continuously administered until the desired change in bone mass or structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with normal bone structure are the desired objectives. For methods of prevention of the present invention, the bisphosphonate compound is continuously
30 administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of bone mass density is often the objective. Nonlimiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the

generally administered about every three to four days. A nonlimiting example of a twice-weekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every Sunday and Wednesday. It is preferred that the unit dosages are not administered on the same or consecutive days, but the twice-weekly dosing regimen can include a dosing regimen in which unit dosages are administered on two consecutive days within a weekly period or on two or more consecutive days falling within two different consecutive weekly periods.

By biweekly dosing is meant that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. In the twice-weekly dosing regimen, each unit dosage is generally administered about every fourteen days. A nonlimiting example of a biweekly dosing regimen would entail the administration of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

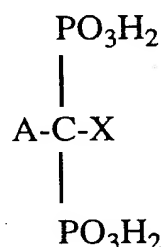
By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period or on two or more consecutive days within two different consecutive monthly periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens

The methods and compositions of the present invention are useful for treating and or preventing the following conditions or disease states: osteoporosis, which can include post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis; Paget's disease; abnormally increased bone turnover; osteomalacia; periodontal disease; localized bone loss associated with periprosthetic osteolysis; and bone fractures.

The methods of the present invention are intended to specifically exclude methods for the treatment and/or prevention of prosthesis loosening and prosthesis migration in mammals as described in PCT application WO 95/30421, to Goodship et al, published November 16, 1995, which is incorporated by reference herein in its entirety.

Bisphosphonates

The methods and compositions of the present invention comprise a bisphosphonate. The bisphosphonates of the present invention correspond to the chemical formula



20

wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C1-C30 substituted alkyl, C1-C10 alkyl or dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl or phenyl substituted thio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those

30

of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit
5 the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 70
10 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

15 Nonlimiting examples of bisphosphonates useful herein include the following :

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

20 Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Patents 4,922,007, to Kieczkowski et al., issued May 1, 1990, and 5,019,651, to Kieczkowski, issued May 28, 1991, both of which are
25 incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

30 1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

Compositions useful in the present invention comprise a pharmaceutically effective amount of a bisphosphonate. The bisphosphonate is typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups, powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Patent No. 5,358,941, to Bechard et al, issued October 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-methacrylamide, and the like.

The precise dosage of the bisphosphonate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the

alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 140 mg of the alendronate compound.

5 Nonlimiting examples of oral compositions comprising alendronate, as well as other bisphosphonates, are illustrated in the Examples, below.

Sequential Administration Of Histamine H2 Receptor Blockers And/Or Proton Pump Inhibitors With Bisphosphonates

10 In further embodiments, the methods and compositions of the present invention can also comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L.J. Hixson, et al.,
15 *Current Trends in the Pharmacotherapy for Peptic Ulcer Disease, Arch. Intern. Med.*, vol. 152, pp. 726-732 (April 1992), which is incorporated by reference herein in its entirety. It has been found in the present invention that the sequential oral administration of a histamine H2 receptor blocker and/or a proton pump inhibitor, followed by a
20 bisphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the bisphosphonate. In more preferred embodiments, the histamine H2 receptor blocker and/or
25 proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the bisphosphate.

The dosage of the histamine H2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

30 Nonlimiting examples of histamine H2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

versus the irritation potential of a low concentration dosage administered for five consecutive days.

The following solutions are prepared :

- (1) simulated gastric juice (pH about 2), i.e. the control solution.
- 5 (2) simulated gastric juice (pH about 2) containing about 0.20 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.
- (3) simulated gastric juice (pH about 2) containing about 0.80 mg/mL of alendronate monosodium trihydrate on an alendronic acid active basis.

10 The simulated gastric juice is prepared by dissolving about 960 mg of pepsin (L-585,228000B003, Fisher Chemical) in about 147 mL of 0.90 (wt %) NaCl (aqueous), adding about 3mL of 1.0 M HCl (aqueous), and adjusting the volume to about 300 mL with deionized water. The pH of
15 the resulting solution is measured and if necessary is adjusted to about 2 using 1.0 M HCl (aqueous) or 1.0 M NaOH (aqueous).

The animals used in the experiments are anesthetized and administered about 50 mL of the appropriate solution over about 30 minutes by infusion into the esophagus using an infusion pump and a
20 rubber catheter. The following treatment experiments are run:

- Group 1: This control group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice [solution (1)] on each of five consecutive days. The animals are sacrificed about 24 hours after the last dose is administered.
- 25 Group 2: This group contains four animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing 0.20 mg/mL of alendronate [solution (2)] on each of five consecutive days. The animals are sacrificed about 24 hours after the last dose is administered.
- 30 Group 3: This group contains five animals. Each animal is administered a dosage of about 50 mL of simulated gastric juice containing 0.80 mg/mL of alendronate [solution (3)] on a single treatment day. The animals are sacrificed about 24 hours after the dose is administered.

Table 1.

Esophageal Irritation Potential Studies				
Group	Alendronate mg/mL	Dosing Schedule	Sacrifice Time	Histo-pathology
1 (n=4)	0	1X daily for 5 days	24 hours after last dosing	Normal. Intact epithelium and absence of inflammatory cells in the submucosa.
2 (n=4)	0.20	1X daily for 5 days	24 hours after last dosing	Deep ulceration of epithelial surface. Marked submucosal inflammation and vacuolation.
3 (n=5)	0.80	1X daily for 1 day	24 hours after dosing	Intact epithelial surface with little submucosal inflammation and vacuolation.
4 (n=5)	0.80	1X daily for 1 day	7 days after dosing	Intact epithelium with either minimal inflammation (2 of 5 animals) or no inflammation (3 of 5 animals) and no vacuolation.

EXAMPLE 2

5

Once-weekly dosing regimen.

Treatment of osteoporosis.

Prevention of osteoporosis.

Alendronate tablets containing about 17.5 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient twice-weekly, preferably about
5 once every three or four days (for example, every Sunday and Wednesday), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient
10 acceptance and compliance.

EXAMPLE 4

Biweekly dosing regimen

15

Treatment of osteoporosis.

Alendronate tablets containing about 140 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient biweekly, i.e. preferably about
20 once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for treating osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

25

Prevention of osteoporosis.

Alendronate tablets containing about 70 mg of alendronate, on an alendronic acid active basis, are prepared (see EXAMPLE 7). A tablet is orally administered to a human patient biweekly, i.e. preferably about
30 once every fourteen days (for example, on alternate Sundays), for a period of at least one year. This method of administration is useful and convenient for preventing osteoporosis and for minimizing adverse gastrointestinal effects, particularly adverse esophageal effects. This method is also useful for improving patient acceptance and compliance.

In yet further embodiments, other bisphosphonate compounds are orally dosed, at the desired dosage, according to the dosing schedules of EXAMPLES 2-5, for treating or preventing osteoporosis or for treating or preventing other conditions associated with abnormal bone resorption.

EXAMPLE 7

10 Bisphosphonate tablets.

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

20	<u>Ingredient</u>	<u>Per Tablet</u>	<u>Per 4000 Tablets</u>
	Alendronate Monosodium Trihydrate	45.68 mg	182.72 g
25	Anhydrous Lactose, NF	71.32 mg	285.28 g
	Microcrystalline Cellulose, NF	80.0 mg	320.0 g
	Magnesium Stearate, NF	1.0 mg	4.0 g
30	Croscarmellose Sodium, NF	2.0 mg	8.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for treating or preventing bone resorption.

WHAT IS CLAIMED IS:

1. An oral method for treating abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to said mammal a pharmaceutically effective amount of a bisphosphonate as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
2. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
3. A method according to claim 1 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.
4. A method according to claim 3 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.
5. A method according to claim 4 wherein said mammal is a human.
6. A method according to claim 5 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.
7. A method according to claim 5 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

14. A method according to claim 12 wherein said bisphosphonate is selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

5

15. A method according to claim 14 wherein said pharmaceutically acceptable salt is alendronate monosodium trihydrate.

10 16. A method according to claim 15 wherein said mammal is a human.

15 17. A method according to claim 16 wherein said dosing interval is once-weekly and said unit dosage comprises about 70 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

18. A method according to claim 16 wherein said dosing interval is twice-weekly and said unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

20 19. A method according to claim 16 wherein said dosing interval is biweekly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

25 20. A method according to claim 16 wherein said dosing interval is twice-monthly and said unit dosage comprises about 140 mg of alendronate monosodium trihydrate, on an alendronic acid active basis.

30 21. A method according to any of claims 12-20 wherein said mammal is an osteoporotic mammal.

22. An oral method for preventing osteoporosis in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising orally administering to

29. A method according to claim 28 wherein said unit dosage comprises about 17.5 mg of the bisphosphonate.

5 30. A method according to claim 28 wherein said unit dosage comprises about 35 mg of the bisphosphonate.

31. A method according to claim 30 wherein said unit dosage is administered once-weekly.

10 32. A method according to claim 28 wherein said unit dosage comprises about 70 mg of the bisphosphonate.

15 33. An oral method for treating abnormal bone resorption in a mammal in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group
20 consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, twice-monthly dosing.

25 34. A method according to claim 33 wherein said histamine H2 blocker or said proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of said bisphosphonate.

30 35. An oral method for preventing abnormal bone resorption in a mammal human in need of such treatment, while minimizing the occurrence of adverse gastrointestinal effects, said method comprising sequentially orally administering to said mammal a pharmaceutically effective amount of a unit dosage of a histamine H2 blocker or a proton pump inhibitor and a unit dosage of a bisphosphonate according to a continuous schedule having a dosing interval selected from the group

FIG. 1

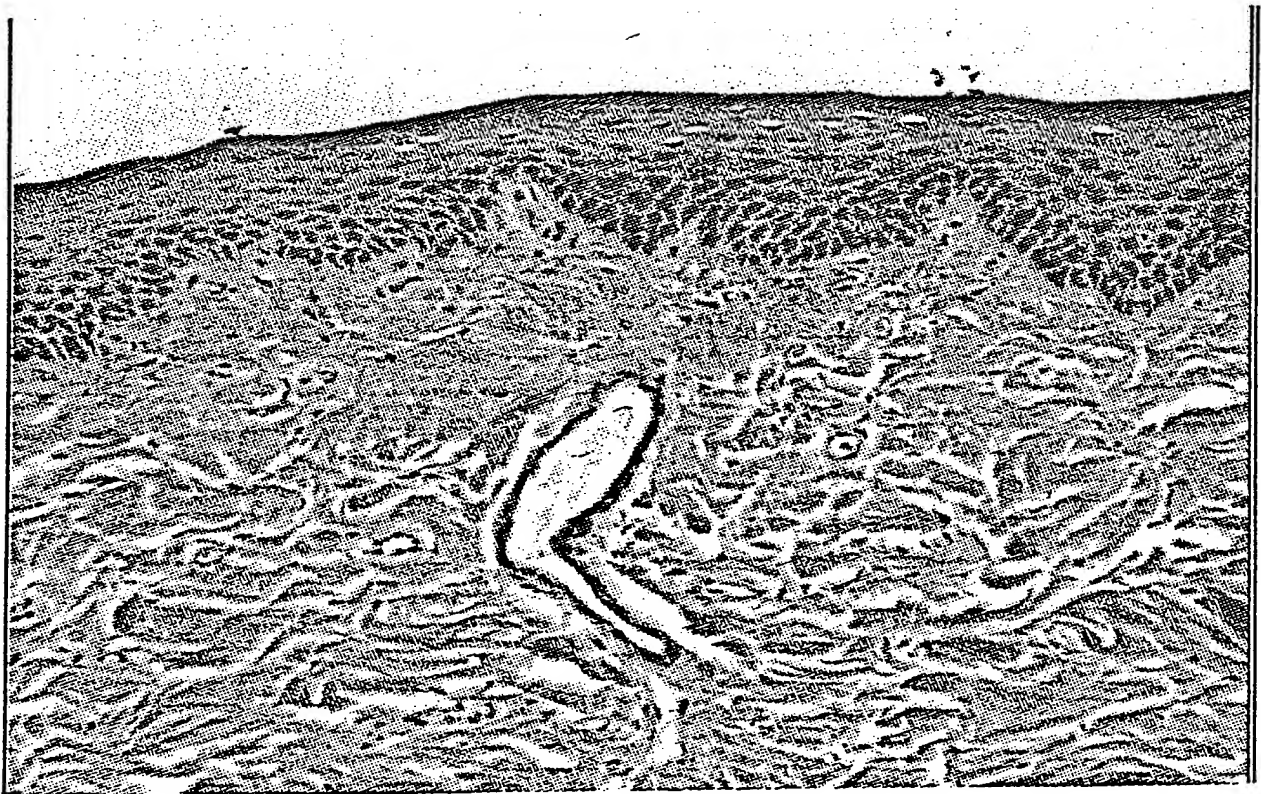


FIG. 2

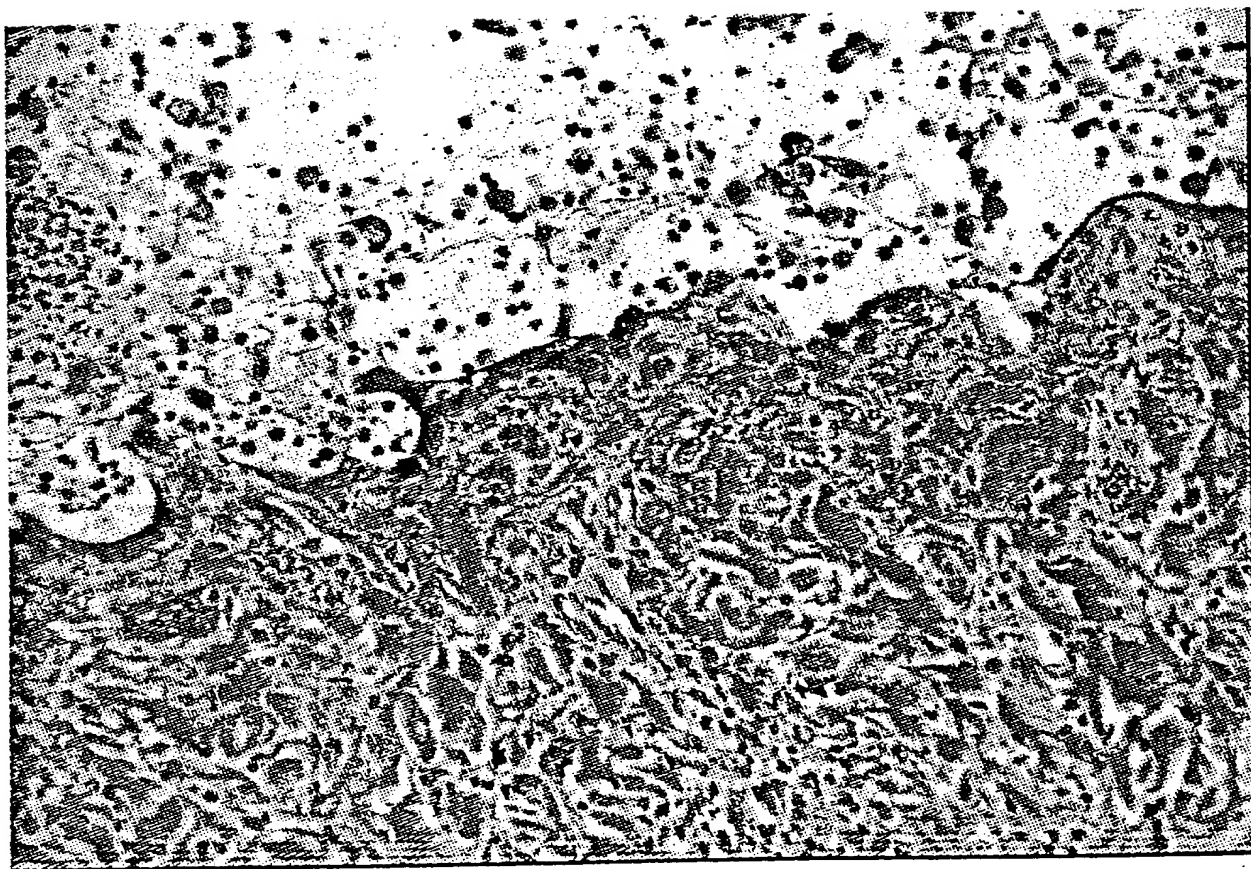


FIG. 3

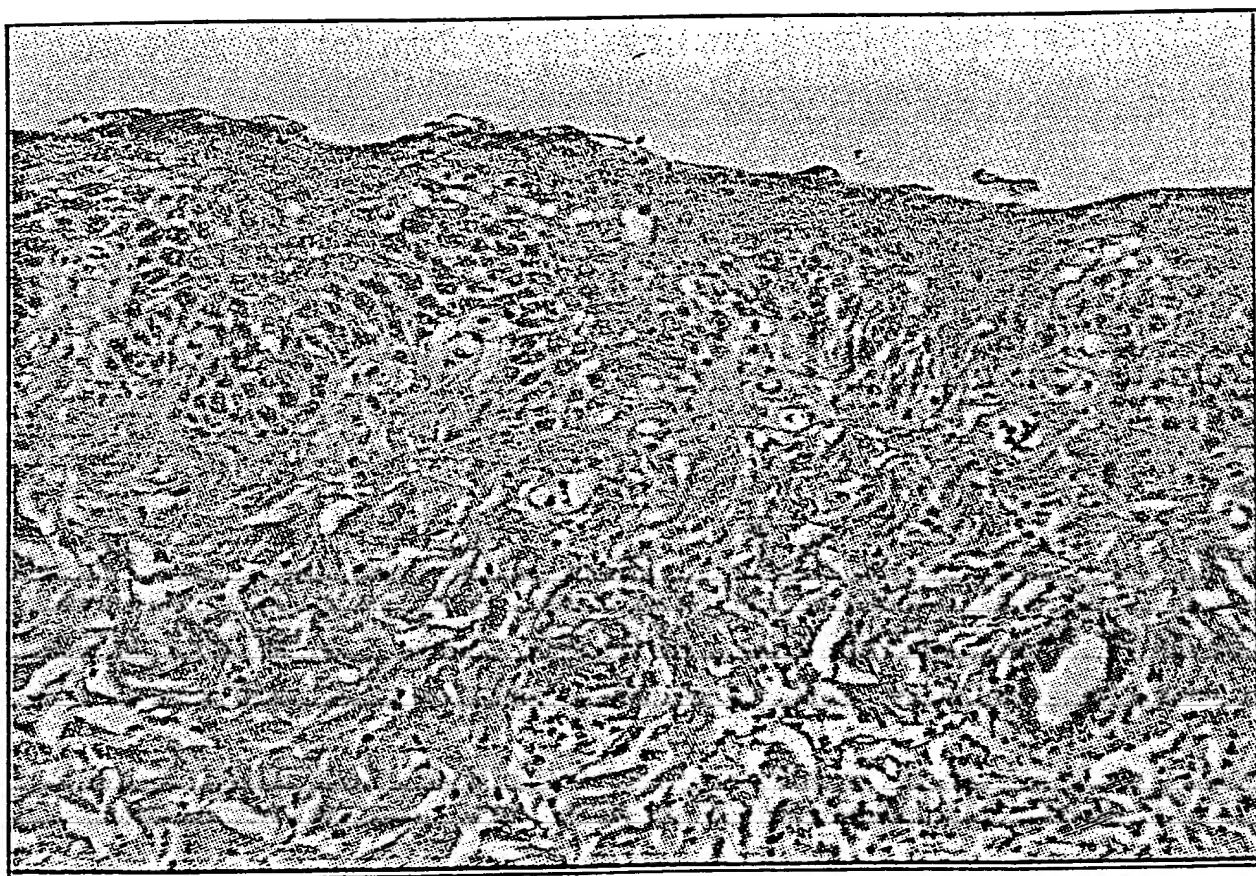
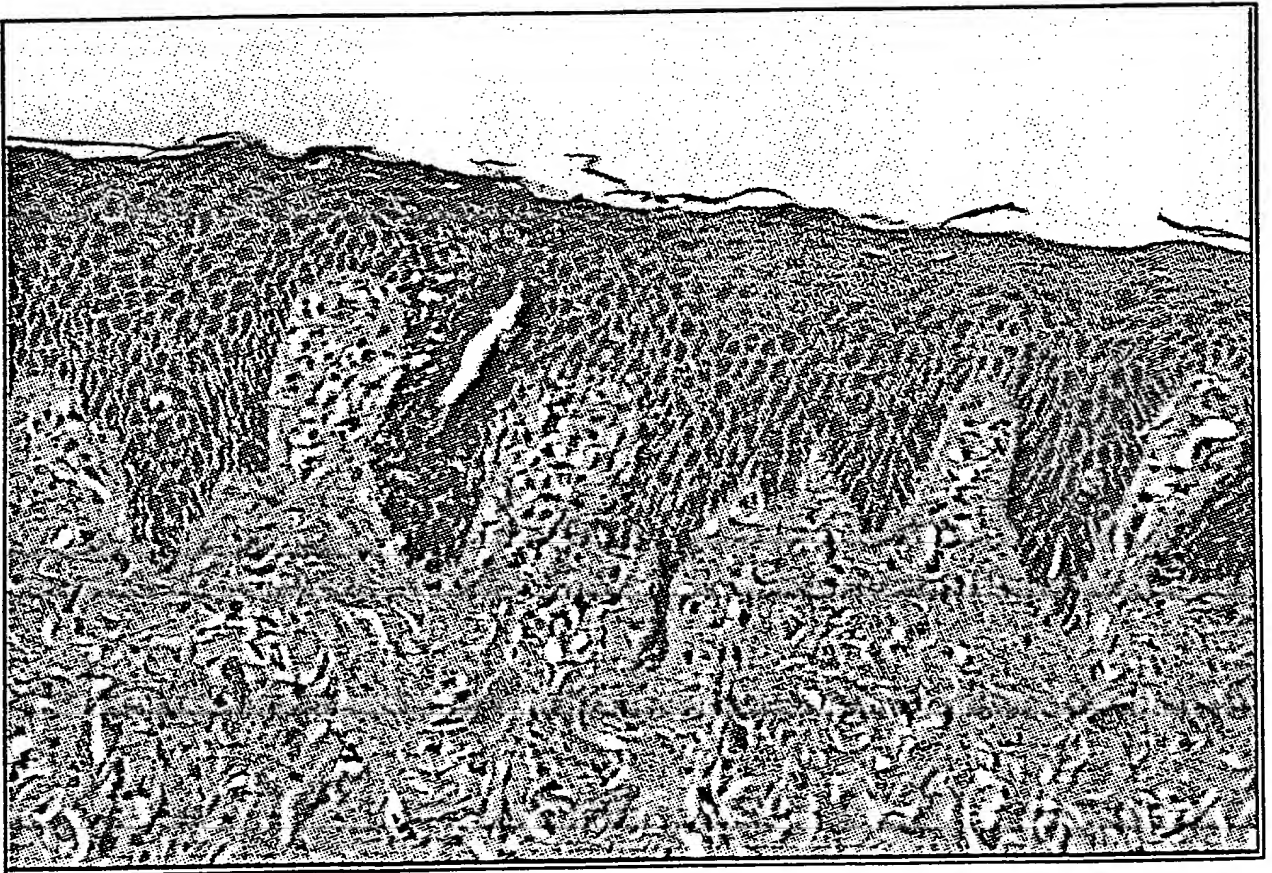


FIG. 4



THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)